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SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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08/319,357 10/06/94 SCHMITT-WILLICH

H SCH1412

EXAMINER

CHAFMAN, L

ART UNIT

PAPER NUMBER

22M2/0309

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2203

DATE MAILED: 03/09/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 10/6/94 12/14/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

- | | |
|---|---|
| 1. <input type="checkbox"/> Notice of References Cited by Examiner, PTO-892. | 2. <input type="checkbox"/> Notice of Draftsman's Patent Drawing Review, PTO-848. |
| 3. <input type="checkbox"/> Notice of Art Cited by Applicant, PTO-1449. | 4. <input type="checkbox"/> Notice of Informal Patent Application, PTO-152. |
| 5. <input type="checkbox"/> Information on How to Effect Drawing Changes, PTO-1474. | 6. <input type="checkbox"/> |

Part II SUMMARY OF ACTION

1. ☒ Claims 2-9, 11, 13, 14, 16, 18-26, 29-39 are pending in the application.
- Of the above, claims — are withdrawn from consideration.
2. ☒ Claims 1, 10, 12, 15, 17, 27, 28 have been cancelled.
3. ☐ Claims — are allowed.
4. ☒ Claims 2-9, 11, 13, 14, 16, 18-26, 29-39 are rejected.
5. ☐ Claims — are objected to.
6. ☐ Claims — are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on —. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-848).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on —, has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed —, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. —; filed on —.
13. ☐ Since this application appears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

1. Applicant's preliminary amendments filed 10/6/94 and 12/14/94 have been entered. Claims 1, 10, 12, 15, 17, 27 and 28 have been cancelled.

2. Claims 14 and 33-35 are rejected under 35 U.S.C. § 112, fourth paragraph, as being of improper dependent form for failing to further limit the subject matter of a previous claim.

Independent claims 14 and 33 are dependent from, respectively, claims 12 and 1 which claims have been cancelled. These claims have been treated on the merits as if they depended from claim 11.

3. Claims 33-35 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

If claim 33 depends from claim 11 as assumed by the examiner, it is vague and indefinite with respect to the compound which is administered because claim 11 requires alkoxy or benzoxy compounds of Formula I yet the compound of claim 33 does not specify such substituents.

4. The following is a quotation of 35 U.S.C. § 103 which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

4. Claims 2-9, 11, 13-14, 16, 18-26, 29-32 and 36-39 are rejected under 35 U.S.C. § 103 as being unpatentable over Berg et al. (EP299,795 or US 5,198,208) in view of Gries et al. (EP 263,059).

Berg et al. disclose DTPA derivatives "particularly useful for the preparations of diagnostic and therapeutic agents for magnetic resonance imaging, scintigraphy, ultrasound imaging, radiotherapy and heavy metal detoxification" (Abstract). The compounds of the Berg et al. invention contain pendant groups designated R1 which correspond to Applicant's Z substituents. Applicant's attention is drawn to the compounds listed on pages 19-22 and particularly to the structure IK on page 21. Berg et al. teach in the Abstract that R1 may be a hydrogen atom, a hydroxyalkyl group, or an optionally hydroxylated alkoxy or alkyloxy group. On page 3, lines 20-30, Berg et al. discuss the metal ions to which the chelate can complex: "It is...particularly preferred that the number of the ion-forming groups X in the compounds of formula I be chosen to equal the valency of the metal species to be chelated by the compound of formula I. Thus, for example, where Gd(III) is to be chelated, the chelating agent of formula I preferably contains three ion-forming X groups...." Although Berg et al. disclose pendant alkyloxy substituents, they do not mention benzoxy substituents such that a benzyl group would be substituted for the alkyl portion of the pendant alkyloxy group.

Gries et al. disclose DTPA derivatives with pendant R1 groups which correspond to Applicant's Z substituents. Applicant's attention is directed to Formula I and the Abstract. Gries et al. teach in the Abstract the equivalence of alkyl groups, phenyl groups, and benzyl groups for the R1 substituent. Possible metals to which the ligands can complex are discussed on page 2 and include metals with atomic numbers of 21-29, 31, 32, 38, 39, 42-44, 49, and 57-83 which are useful for diagnostic purposes. Thus, since Gries et al. and Berg et al. both teach DTPA derivatives which complex with Gd and which are used for diagnosis, it would have been obvious to a person of ordinary skill in the art to utilize the teaching of Gries et al. to modify the invention of Berg et al. with an equivalent hydrocarbon group for the alkyl portion of the pendant alkyloxy group.

Furthermore, case precedent has held the equivalence of benzyl and alkyl groups: "Cyclo-lower-alkyl and phenyl radicals are so extremely common that we believe any chemist of ordinary competence would readily realize that said radicals might be substituted for...alkyl radicals" (Ex parte Koster, 136 USPQ 75). Thus, benzoxy and alkyloxy groups are believed to be equivalent structures to the ordinarily skilled organic chemist, and substituting one for the other would have been readily obvious to this artisan at the time of applicant's invention.

5. Claims 33-35 are rejected under 35 U.S.C. § 103 as being unpatentable over Gries et al. ^(US Pat. 4,647,447) in view of Lauffer (US 4,880,008).

Gries et al. disclose DTPA complexes with paramagnetic metal ions for use in NMR imaging. Applicants' attention is directed to columns 1-2 where in Formula I, A is $-\text{CH}_2-\text{CH}_2(\text{ZCH}_2-\text{CH}_2)_m-$ and the Example in columns 11-12. Gries et al. do not teach that a phenyl ring is substituted on one of the mid-chain carbons. Lauffer teaches the enhancement of NMR imaging by administering a paramagnetic metal ion complexed with a chelating substance which complex binds non-covalently to targets such as proteins. See column 1, lines 18-56. In column 3, lines 4-22, Lauffer teaches "Protein binding is provided for by the incorporation of hydrophobic groups into the agent....Where the target is a protein, lipophilicity enhances binding of contrast agents to the protein. Lipophilicity is provided by a non-polar structure, the presence of at least one aryl group (e.g., a substituted or unsubstituted phenyl ring).... Applicants' attention is further directed to column 7, line 63-column 8, line 10 as well as claim 6 where DTPA derivatives are shown. Thus, to a person of ordinary skill in the art at the time of applicants' invention, it would have been obvious to substitute a hydrophobic, lipophilic substituent such as a phenyl ring on the DTPA compounds of Gries et al. in order to gain the advantage taught in Lauffer, namely enhanced non-covalent protein binding. Since both patents teach NMR imaging with DTPA, it would have been prima facie obvious to utilize the teaching of Lauffer in the invention of Gries et al. It further would have been obvious to limit the number of phenyl substituents for steric

Serial Number: 8/319,357
Art Unit: 2203

-5-

considerations, specifically that two phenyl groups on adjacent carbon atoms would crowd the molecule.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Lara Chapman whose telephone number is (703) 308-0450 or her supervisor Gary Geist who can be reached at (703) 308-1701.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0511.

Art Unit 2203 will move to Group 1200 on April 2, 1995. After April 2nd, any written communication should be designated with Group 1200, and any telephone communication should be routed through the Group 1200 receptionist as (703) 308-1235.



GARY L. GEIST
SUPERVISORY PATENT EXAMINER
GROUP 2200



LARA CHAPMAN,
PATENT EXAMINER
GROUP 2200

March 3, 1995